201-15754B

I U C L I D

Data Set

Existing Chemical	:	ID: 107-30-2
CAS No.	:	107-30-2
Producer related part		
Company	:	Dow Chemical, TERC
Creation date	:	28.05.2004
Substance related part		
Company	:	Dow Chemical, TERC
Creation date	:	28.05.2004
Status	:	
Memo	:	
Printing date	:	17.12.2004
Revision date	:	
Date of last update	:	16.08.2004
Number of pages	:	53
Chapter (profile)	:	Chapter: 1, 2, 3, 4, 5, 6, 7, 8, 10
Reliability (profile)	:	Reliability: without reliability, 1, 2, 3, 4
Flags (profile)	:	Flags: without flag, confidential, non confidential, WGK (DE), TA-Luft (DE), Material Safety Dataset, Risk Assessment, Directive 67/548/EEC, SIDS

1.0.1 APPLICANT AND COMPANY INFORMATION

1.0.2 LOCATION OF PRODUCTION SITE, IMPORTER OR FORMULATOR

1.0.3 IDENTITY OF RECIPIENTS

1.0.4 DETAILS ON CATEGORY/TEMPLATE

1.1.0 SUBSTANCE IDENTIFICATION

1.1.1 GENERAL SUBSTANCE INFORMATION

Purity type :
Substance type : organic
Physical status : liquid
Purity : >= 92 % w/w
Colour :
Odour :

Reliability : (2) valid with restrictions
22.07.2004 (1)

1.1.2 SPECTRA

1.2 SYNONYMS AND TRADENAMES

1.3 IMPURITIES

Purity :
CAS-No : 542-88-1
EC-No :
EINECS-Name : bis (chloromethyl) ether
Molecular formula :
Value : >= 1 - 8 % w/w

Remark : According to the American Industrial Hygiene Association, bis(chloromethyl) ether, BCME, is formed inadvertently in the production and use of CMME. In the presence of either hydrogen or hydroxyl ions and traces of water, CMME disproportionates to aldehydes and dimethoxymethane, which, in turn, recombine to form BCME.
22.07.2004 (1)

Purity :
CAS-No : 542-88-1
EC-No : 208-832-8
EINECS-Name :
Molecular formula :

Value : < 1 % v/v

Remark : Current production material contains much lower impurities of bis-chloromethyl ether.

22.07.2004

1.4 ADDITIVES

1.5 TOTAL QUANTITY

1.6.1 LABELLING

1.6.2 CLASSIFICATION

Result : Without establishing a PEL, OSHA identifies CMME as an occupational carcinogen and regulates worker exposure.

22.07.2004 (2)

Result : Category 1, sufficient evidence of carcinogenicity for humans

10.06.2004 (3)

Result : Carcinogen with no further classification

22.04.2003 (4)

Result : Group 1, known carcinogen for which there is sufficient evidence of carcinogenicity from studies in humans

22.04.2003 (5)

Result : A2, suspected human carcinogen

10.06.2004 (6)

1.6.3 PACKAGING

1.7 USE PATTERN

1.7.1 DETAILED USE PATTERN

1.7.2 METHODS OF MANUFACTURE

1.8 REGULATORY MEASURES

1.8.1 OCCUPATIONAL EXPOSURE LIMIT VALUES

Type of limit : TLV (US)
Limit value :

Result : ACGIH TLV-TWA for bis(chloromethyl) ether is 0.001 ppm (0.0047 mg/m3) A1 (confirmed human carcinogen).
22.07.2004 (7)

Type of limit : other: Dow Industrial Hygiene Guideline
Limit value : 100 other: ppb
Short term exposure limit value
Limit value :
Time schedule : 8 hour(s)
Frequency : times

29.06.2004 (8)

1.8.2 ACCEPTABLE RESIDUES LEVELS

1.8.3 WATER POLLUTION

1.8.4 MAJOR ACCIDENT HAZARDS

1.8.5 AIR POLLUTION

1.8.6 LISTINGS E.G. CHEMICAL INVENTORIES

1.9.1 DEGRADATION/TRANSFORMATION PRODUCTS

1.9.2 COMPONENTS

1.10 SOURCE OF EXPOSURE

1.11 ADDITIONAL REMARKS

1.12 LAST LITERATURE SEARCH

1.13 REVIEWS

2.1 MELTING POINT

Value	:	= -103.5 °C
Sublimation	:	
Method	:	
Year	:	1983
GLP	:	no data
Test substance	:	
Reliability	:	(2) valid with restrictions

01.04.2003 (9)

2.2 BOILING POINT

Value	:	= 59 °C at
Decomposition	:	
Method	:	
Year	:	1983
GLP	:	no data
Test substance	:	
Reliability	:	(2) valid with restrictions

01.04.2003 (9)

Value	:	= 59.5 °C at
Decomposition	:	
Method	:	
Year	:	1983
GLP	:	
Test substance	:	as prescribed by 1.1 - 1.4
Reliability	:	(2) valid with restrictions

01.04.2003 (10)

2.3 DENSITY

Type	:	relative density
Value	:	= 1.0625 at 4 °C
Reliability	:	(2) valid with restrictions

09.06.2003 (11)

2.3.1 GRANULOMETRY

2.4 VAPOUR PRESSURE

Value	:	= 162.7 hPa at 20 °C
Decomposition	:	
Method	:	
Year	:	1977
GLP	:	
Test substance	:	as prescribed by 1.1 - 1.4

01.04.2003 (12)

Value	:	= 286.6 hPa at 25 °C
Decomposition	:	
Method	:	
Year	:	1988
GLP	:	
Test substance	:	as prescribed by 1.1 - 1.4
Remark	:	No further information provided
Reliability	:	(2) valid with restrictions

01.04.2003 (13)

2.5 PARTITION COEFFICIENT

Partition coefficient	:	
Log pow	:	= -.21 at °C
pH value	:	
Method	:	
Year	:	1977
GLP	:	no data
Test substance	:	
Remark	:	Value calculated from the parent solute and the known additive pi constants for substituents or by summation of fragmental constants. No additional information supplied. Log Kow is probably not applicable due to the rapid hydrolysis of this material.
Reliability	:	(4) not assignable 4E

20.05.2003 (14)

2.6.1 SOLUBILITY IN DIFFERENT MEDIA

Remark	:	At a concentration <50% water solubility (concentration not stated) the half life was 2 minutes. Water solubility is probably not applicable due to the rapid hydrolysis of this material.
Reliability	:	(2) valid with restrictions

17.06.2003 (15)

Deg. product	:	
Method	:	
Year	:	1979
GLP	:	no data
Test substance	:	as prescribed by 1.1 - 1.4
Remark	:	Hydrolyzes rapidly in water with a half life of <1 second. Water solubility is probably not applicable due to the rapid hydrolysis of this material.
Reliability	:	(2) valid with restrictions

17.06.2003 (16)

2.6.2 SURFACE TENSION

2.7 FLASH POINT

2.8 AUTO FLAMMABILITY

2.9 FLAMMABILITY

2.10 EXPLOSIVE PROPERTIES

2.11 OXIDIZING PROPERTIES

2.12 DISSOCIATION CONSTANT

2.13 VISCOSITY

2.14 ADDITIONAL REMARKS

3.1.1 PHOTODEGRADATION

Type	:	air
Light source	:	
Light spectrum	:	nm
Relative intensity	:	based on intensity of sunlight
Method	:	Method of Hendry, D.G. and Kenley, R.A.(1979). Atmospheric reaction products of organic compounds. EPA Report EPA-560/12-79-001 was used.
Result	:	The atmospheric residence time is expected to be 0.004 - 3.9 days. This is based on theoretically-estimated gas-phase rate constants for the initial reaction between OH radicals and the volatile chemical in units of 10(-12)cm3/molecule/second. The Koh rate constant for CMME is estimated to be 3.
Reliability	:	(2) valid with restrictions 2E

09.06.2004 (17)

Type	:	air
Light source	:	
Light spectrum	:	nm
Relative intensity	:	based on intensity of sunlight
Result	:	1.0 x 10-10 mol-1.sec-1
Reliability	:	(2) valid with restrictions 2F

09.06.2004 (12)

3.1.2 STABILITY IN WATER

Type	:	abiotic
t1/2 pH4	:	at °C
t1/2 pH7	:	at °C
t1/2 pH9	:	at °C
Deg. product	:	
Method	:	
Year	:	1977
GLP	:	no data
Test substance	:	as prescribed by 1.1 - 1.4
Result	:	Half life is <0.007 seconds in water. In the vapor phase at 25C and 70% relative humidity, the half life for 100 ppm and 1000 ppm CMME is 6 minutes and 3.5 minutes, respectively,
Reliability	:	(2) valid with restrictions 2E

29.06.2004 (18) (12)

Type	:	abiotic
t1/2 pH4	:	at °C
t1/2 pH7	:	at °C
t1/2 pH9	:	at °C
Method	:	Known quantities (10-50 ul) were added to a titration vessel containing 10 ml solvent (water:dimethylformamide, 3:1). Hydrolysis and titrations were done in a constant temperature bath at 0C by use of an automatic recording pH titrator (Radiometer Co., Copenhagen, Denmark) set to

maintain pH 7.0 by the automatic addition of 2.0N aqueous sodium hydroxide. Pseudo first-order rate constants were calculated from the amount of base added over a known time interval.

Result : The half life was less than 2 minutes.
Reliability : (2) valid with restrictions
2e

29.06.2004 (19)

Type : abiotic
t1/2 pH4 : at °C
t1/2 pH7 : at °C
t1/2 pH9 : at °C

Result : Chloromethyl methyl ether is hydrolyzed to hydrogen chloride, methanol and formaldehyde.
Reliability : (2) valid with restrictions
29.06.2004 (20)

3.1.3 STABILITY IN SOIL

3.2.1 MONITORING DATA

3.2.2 FIELD STUDIES

3.3.1 TRANSPORT BETWEEN ENVIRONMENTAL COMPARTMENTS

Type : fugacity model level I
Media :
Air : % (Fugacity Model Level I)
Water : % (Fugacity Model Level I)
Soil : % (Fugacity Model Level I)
Biota : % (Fugacity Model Level II/III)
Soil : % (Fugacity Model Level II/III)
Method :
Year :

Method : Level I Fugacity Model version 2.11, Obtained from the Canadian Environmental Modeling Centre, Trent University, Peterborough, Ontario, Canada

Input Parameters for Level I Model

Property	Value	Source
Data Temperature (°C)	25	Default environmental temperature
Chemical Type	1	Type 1 indicates chemical can partition into all environmental compartments
Molecular Mass (g/mol)	80.51	Calculated from molecular structure
Water Solubility (g/m3)	69,440	Estimated using QSAR [1]
Vapor Pressure @ 25° C (Pa)	28,660	Measured value [2]
Melting Point (°C)	-103.5	Measured value [2]
Estimated Henry's Law Constant (H) (Pa m3/mol)	33.2	Calculated by Level I Fugacity Model [3]
Log Kow Octanol-Water Partition Coefficient	0.32	Estimated using QSAR [1]

Simulated Emission (kg) 100,000 Level I Default Value [3]
Simulated environment Default Level I environment [3]

REFERENCES

1. U.S. EPA. 2003. EPI Suite software, version v3.11. United States Environmental Protection Agency, Office of Pollution Prevention and Toxics, Washington, D. C. Available at: http://www.epa.gov/oppt/exposure/docs/episuitedl.htm
2. AIChE. 2002. Design Institute for Physical Properties Research (DIPPR) Database, American Institute of Chemical Engineers, New York, NY.
3. Mackay, D., 2001. Multimedia Environmental Models: The Fugacity Approach. Lewis Publishers, CRC Press, Boca Raton, FL. Models available at: http://www.trentu.ca/cemc/models.html

Remark : Due to instantaneous reaction in water, water solubility and log Kow cannot be measured for this material. Values for these required model inputs were estimated using accepted quantitative structure-activity relationships (QSAR) [1].

Result : Predicted equilibrium distribution among air, water, soil, and sediments

Emission Scenario	Percentage and amount distributed to Air	Water	Soil	Sediment
100,000 kg (total emissions)	87.0% 87000kg	13.0% 13000kg	0.024% 24.0kg	0.00053% 0.5kg

Conclusion : In the absence of advective and reactive processes, these physical properties indicate that the material would be distributed primarily to the atmosphere (87%) and at a lesser extent to water (13%) at equilibrium. Note however that this material cannot exist in water, and will also be rapidly reacted in the atmosphere.

Reliability : (2) valid with restrictions
2f: Accepted calculation method

09.08.2004

Type : fugacity model level III
Media :
Air : % (Fugacity Model Level I)
Water : % (Fugacity Model Level I)
Soil : % (Fugacity Model Level I)
Biota : % (Fugacity Model Level II/III)
Soil : % (Fugacity Model Level II/III)
Method :
Year :

Method : Level III Fugacity Model version 2.70. Obtained from the Canadian Environmental Modeling Centre, Trent University, Peterborough, Ontario, Canada

Input Parameters for Level III Model

Property	Value	Source
Data Temperature (°C)	25	Default environmental temperature
Chemical Type	1	Type 1 indicates chemical can partition into all environmental compartments
Molecular Mass (g/mol)	80.51	Calculated from molecular structure
Water Solubility (g/m3)	69,440	Estimated using QSAR [1]
Vapor Pressure @ 25° C (Pa)	28,660	Measured value [2]
Melting Point (°C)	-103.5	Measured value [2]
Estimated Henry's Law Constant (H) (Pa m3/mol)	33.2	Calculated by Level I Fugacity Model [3]

Log Kow Octanol-Water Partition Coefficient		0.32	Estimated using QSAR [1]
Reaction Half-lives	(hr.)		Input to Level III Model
Air (vapor phase)		7.0	Measured half-life for reaction with water vapor [4]
Water (no susp. solids)		0.00028	Measured hydrolysis half-life in water [5]
Soil		7.0	Based on half-life for reaction with water vapor [4]
Sediment		*1.0 x 10(11)	Material cannot exist in water
Suspended Sediment		*1.0 x 10(11)	Material cannot exist in water
Fish		*1.0 x 10(11)	Material cannot exist in water
Aerosol		*1.0 x 10(11)	Aerosol emissions not expected

*Default value used in Level III model when reaction is expected to be negligible in this compartment

REFERENCES

1. U.S. EPA. 2003. EPI Suite software, version v3.11. United States Environmental Protection Agency, Office of Pollution Prevention and Toxics, Washington, D. C. Available at: http://www.epa.gov/oppt/exposure/docs/episuitedl.htm
2. AIChE. 2002. Design Institute for Physical Properties Research (DIPPR) Database, American Institute of Chemical Engineers, New York, NY.
3. Mackay, D., 2001. Multimedia Environmental Models: The Fugacity Approach. Lewis Publishers, CRC Press, Boca Raton, FL. Models available at: http://www.trentu.ca/cemc/models.html
4. Tou, J. C. and Kallos, G. J. 1974. Kinetic study of the stabilities of chloromethyl methyl ether and bis(chloromethyl) ether in humid air. Analytical Chemistry 46:1866-1869.
5. Nichols, R.W. and Merritt, R.F. (1973). Relative solvolytic reactivities of chloromethyl ether and bis(chloromethyl)ether. J. Natl Cancer Inst. 50:1373-1374.

Remark : Due to instantaneous reaction in water, water solubility and log Kow cannot be measured for this material. Values for these required model inputs were estimated using accepted quantitative structure-activity relationships (QSAR) [1]. Variation of input water solubility from 100 to 1.0 x 106 g/m3, and log Kow from -1 to 3.0 was shown to have little or no effect on output of the Level III model. Since emissions of this material to water and soil are not possible, a single emission scenario of 1,000 kg/hr. in air was used.

Result : Distribution among air, water, soil, and sediments

Emission Scenario	Percentage and amount distributed to Air	Water	Soil	Sediment	Residence Time (days) [without advection in brackets]
1,000 kg/hr to Air	100.0% 1700kg	0.0000019% 0.000032kg	0.042% 0.7kg	0.00000000079% 0.000000013kg	0.07 [0.42]

Conclusion : The results of Level III fugacity modeling indicate that emissions of this substance to the atmosphere will remain in the atmosphere, and will be rapidly destroyed through hydrolytic and photolytic reactions.

Reliability : (2) valid with restrictions
2f: Accepted calculation method

09.08.2004

3.3.2 DISTRIBUTION

3.4 MODE OF DEGRADATION IN ACTUAL USE

3.5 BIODEGRADATION

Type	:	aerobic
Inoculum	:	activated sludge
Concentration	:	100 mg/l related to related to
Contact time	:	28 day(s)
Degradation	:	(±) % after
Result	:	readily biodegradable
Deg. product	:	
Method	:	OECD Guide-line 301 C "Ready Biodegradability: Modified MITI Test (I)"
Year	:	1992
GLP	:	no data
Test substance	:	as prescribed by 1.1 - 1.4
Remark	:	Based on this data, the test material is considered to be readily biodegradable.
Result	:	In three replicates of the test, 33, 67 and 76% BOD was observed. These values corresponded to 80, 80 and 83% of the TOC.
Reliability	:	(2) valid with restrictions

09.06.2004 (21)

3.6 BOD5, COD OR BOD5/COD RATIO

3.7 BIOACCUMULATION

3.8 ADDITIONAL REMARKS

Memo	:	half life in air
Method	:	Rate of hydrolysis was determined under various experimental conditions using several materials.
Result	:	The rate of hydrolysis ranged between 0.31 - 0.0018 per minute (half lifes ranged from 2.3 - 390 minutes) and was dependent on the surface of the chamber, temperature and relative humidity. As the temperature increased the rate of hydrolysis decreased. This suggests that the hydrolysis reaction occurred on the glass surface instead of in the gas phase. A strong surface effect on the rate of hydrolysis was observed in the following decreasing order: ferric oxide powder-coated Saran > glass >Teflon >Saran. Therefore the hydrolysis half-life in gas phase was greater than or equal to 390 minutes at a relative humidity of 39% at 29C. The rate of hydrolysis was slower at lower relative humidities. Because of the strong surface effect on the rate of hydrolysis of CMME, the material of construction of the analytical devices used had a significant effect on the results.
Reliability	:	(2) valid with restrictions 2E

19.05.2003 (22)

Memo	:	Half life in air
Result	:	Half life is <3.9 days. Hydrolysis products are hydrogen chloride, methanol

and formaldehyde.
01.04.2003 (23)

Memo : Stability in air

Result : Half life in air due to hydrolysis is 3.5 to 6 minutes at 25C.
01.04.2003 (24)

4.1 ACUTE/PROLONGED TOXICITY TO FISH

Type	:	flow through
Species	:	Ictalurus melas (Fish, fresh water)
Exposure period	:	96 hour(s)
Unit	:	mg/l
LC50	:	= 24.8
Limit test	:	
Analytical monitoring	:	no
Method	:	other: acute toxicity test "flow through bioassay"
Year	:	1977
GLP	:	no
Test substance	:	other TS: formalin, commercial grade, 37%
Remark	:	fingerlings; pH 6.5, water hardness 8, water temperature 12 degrees C. Robust summary essentially copied from UNEP dossier (2 Sept 2003) for formaldehyde.
Test substance	:	Test substance, formaldehyde, is a breakdown product of CMME
Reliability	:	(2) valid with restrictions 2e: Meets generally accepted scientific standards, well-documented and acceptable for assessment

06.07.2004 (25)

Type	:	flow through
Species	:	Lepomis macrochirus (Fish, fresh water)
Exposure period	:	96 hour(s)
Unit	:	mg/l
LC50	:	= 15400
Method	:	other
Year	:	
GLP	:	
Test substance	:	other TS: methanol purity not stated
Remark	:	Flow through acute toxicity test. EC50: median effect concentration, EC50 = 12,700 mg/L Robust summary essentially copied from existing IUCLID dossier for methanol. LC50 is lowest 96 hr flow-through value cited in dossier.
Test substance	:	Test substance, methanol, is a breakdown product of CMME
Reliability	:	(2) valid with restrictions 2e Meets generally accepted scientific standards, well-documented and acceptable for assessment

02.07.2004 (26)

Type	:	semistatic
Species	:	Cyprinus carpio (Fish, fresh water)
Exposure period	:	96 hour(s)
Unit	:	
LC50	:	= 4.3
Limit test	:	
Analytical monitoring	:	yes
Method	:	OECD Guide-line 203 "Fish, Acute Toxicity Test"
Year	:	1992
GLP	:	no
Test substance	:	other TS: 12N (37.2%) hydrochloric acid
Method	:	Test Organisms: a) Average Size: 4.6+/-0.3 cm in body length, 1.1+/-0.1 g in body weight b) Pretreatment: acclimated for 7 days before testing; any groups showing >5% mortality during this period were not used for testing, fish were

selected at random.
c) Supplier/Source: Sugishima fish hatchery in Kumamoto prefecture, Japan
Test Conditions:
a) Dilution Water Source: Dechlorinated tap water
b) Dilution Water Chemistry: Hardness: 52.0 mg/L as CaCO3; alkalinity: 33.0 mg/L as CaCO3, ph: 7.5, DO: 8.4
c) Exposure Vessel Type: 50-L glass tank (60 x 29.5 x 36 cm)
d) Nominal Concentrations: Five pH series (4.0, 4.5, 5.0, 5.5 and 6.0) and a dilution water control were tested.
e) Stock and Test Solutions: The dilution water was added into the test vessel and the test solutions were prepared by adjusting to desired pH with hydrochloric acid.
f) Number of Replicates, fish per replicate: 1, 10 fish per replicate
g) Renewal Rate of Test Water: Renewed once per day
h) Water Temperature Range: 23.0+/-2C (containers used for testing were placed in an incubator)
i) Light Condition: 16h:8h light-darkness cycle
Statistical Method:
a) Data Analysis: Graphical method using logarithmic probability paper

Remark : It is the resulting pH rather than the concentration of HCl that determines lethality toward aquatic life (Environment Canada, 1984). In general, a pH lower than 5 is lethal to most fish, although specialized aquatic flora and fauna may develop. Due to different buffering capacities of the water used for several studies, the acute fish LC50 values ranged from 4.92 to 282 mg/L.

Robust summary essentially copied from existing IUCLID dossier for HCl (August 9, 2002). LC50 is lowest 96 hr valid value cited in dossier.

Reference:
Enviro Technical Information For Problem Spills (1984) Hydrogen Chloride/Hydrochloric Acid, Environment Canada Environmental Protection Service

Result : Measured concentrations (as mg/L): Not described
Water chemistry in Test: DO=7.2-8.4 mg/L; Temperature = 23.0-24.2C
All fish died at a pH of 4.0 and all fish survived at a pH of 4.5.

A pH of 4.3 corresponds to 4.92 mg/L

Test substance : Test substance, hydrogen chloride, is a breakdown product of CMME

Reliability : (2) valid with restrictions
2d: Meets national standard methods with acceptable restrictions

06.07.2004 (27)

4.2 ACUTE TOXICITY TO AQUATIC INVERTEBRATES

Type	:	
Species	:	Daphnia pulex (Crustacea)
Exposure period	:	48 hour(s)
Unit	:	mg/l
EC50	:	= 5.8
Method	:	other: according to the OECD standard
Year	:	
GLP	:	no data
Test substance	:	other TS: formaldehyde 37% purity

Remark : Robust summary essentially copied from existing IUCLID dossier for formaldehyde. Value is only 48 hr value cited for daphnids.

Result : 48 hr EC50 = 5.8 (Confidence intervals 4.3 - 7.8).

Test condition	:	Test temperature 20 +/- 1C, the standard stock solutions were prepared according to Standard Methods: APHA-AWWA-WEF, 1992 and Leithe, 1974, daphnids cultured in 3 L aquariums and beakers were illuminated for 12 hrs/day.
Test substance	:	Test substance, formaldehyde, is a breakdown product of CMME.
Reliability	:	(2) valid with restrictions 2e: Meets generally accepted scientific standards, well-documented and acceptable for assessment

06.07.2004 (28)

Type	:	
Species	:	Daphnia sp. (Crustacea)
Exposure period	:	48 hour(s)
Unit	:	mg/l
NOEC	:	= 10000
Method	:	
Year	:	
GLP	:	no data
Test substance	:	other TS: methanol purity not stated

Remark	:	Robust summary essentially copied from existing IUCLID dossier for methanol. Value is only 48 hr value cited for daphnids.
Test substance	:	Test substance, methanol, is a breakdown product of CMME
Reliability	:	(2) valid with restrictions 2e: Meets generally accepted scientific standards, well-documented and acceptable for assessment

02.07.2004 (29)

Type	:	
Species	:	Daphnia magna (Crustacea)
Exposure period	:	48 hour(s)
Unit	:	mg/l
EC50	:	= 0.492
Analytical monitoring	:	yes
Method	:	OECD Guide-line 202
Year	:	
GLP	:	
Test substance	:	other TS: 12N (37.2%) hydrochloric acid

Method :

Test Organisms:
a) Age at study initiation: neonates (<24 hr old)
b) Supplier/Source: Laboratory bred daphnids which were basically supplied by the University of Sheffield (Sheffield S10 2UQ, UK) were used.
Test Conditions:
a) Dilution Water Source: Dechlorinated tap water
b) Dilution Water Chemistry: Hardness: 52.0 mg/L as CaCO3; alkalinity: 33.0 mg/L as CaCO3, pH: 7.5, DO: 8.4
c) Exposure Vessel Type: 200 mL test solution in a 250 mL glass beaker; 4 beakers per treatment
d) Nominal Concentrations: Five pH series (4.0, 4.5, 5.0, 5.5 and 6.0) and a dilution water control were tested
e) Stock and Test solutions: The dilution water was added into the test vessel and the test solutions were prepared by adjusting to desired pH with hydrochloric acid.
f) Number of Replicates: 4 replicates
g) Individuals per Replicates: 5 daphnids per replicate
h) Renewal Rate of Test Water: Renewed once a day
i) Water Temperature Range: 20.0+/-1C (Containers used for testing were placed in an incubator)
j) Light Condition: <1200 lx, 16 h:8 h light-darkness cycle
Statistical Method

		a) Data Analysis: Graphical method using logarithmic probability paper
Remark	:	It is the resulting pH rather than the concentration of HCl that determines lethality toward aquatic life (Environment Canada, 1984). In general, a pH lower than 5 is lethal to most fish, although specialized aquatic flora and fauna may develop. Robust summary essentially copied from existing IUCLID dossier for hydrogen chloride (August 9, 2002). Value is only 48 hr value cited for daphnids. Reference: Enviro Technical Information For Problem Spills (1984) Hydrogen Chloride/Hydrochloric Acid, Environment Canada Environmental Protection Service
Result	:	Water chemistry in Test: DO=8.7-8.8 mg/L; Temperature =20.1=20.5C Cumulative immobilization: no immobilization was observed at pHs of 5.5 and 6.0 at 3, 24 or 48 hours. At a pH of 5.0, no immobilization was noted after 3 hours but 11 of 20 daphnids were immobilized after 24 hours and all were immobilized after 48 hours. At a pH of 4.5, 4 of 20 were immobilized after 3 hours and all were immobilized after 24 and 48 hours. At a pH of 4.0, all were immobilized after 3 hours. A pH of 5.3 corresponds to 0.492 mg/L of 12N HCl.
Test substance	:	Test substance, hydrogen chloride, is a breakdown product of CMME
Reliability	:	(2) valid with restrictions 2d: Meets national standard methods with acceptable restrictions

06.07.2004 (27)

4.3 TOXICITY TO AQUATIC PLANTS E.G. ALGAE

Species	:	Microcystis aeruginosa (Algae, blue, cyanobacteria)
Endpoint	:	
Exposure period	:	7 day(s)
Unit	:	mg/l
EC0	:	= 530
Method	:	
Year	:	
GLP	:	no data
Test substance	:	other TS: methanol purity not stated
Remark	:	Robust summary essentially copied from existing IUCLID dossier for methanol. Value is lowest 7 day value.
Test substance	:	Test substance, methanol, is a breakdown product of CMME
Reliability	:	(2) valid with restrictions 2e: Meets generally accepted scientific standards, well-documented and acceptable for assessment

02.07.2004 (30)

Species	:	Scenedesmus quadricauda (Algae)
Endpoint	:	biomass
Exposure period	:	192 hour(s)
Unit	:	mg/l
toxicity threshold	:	= 2.5
Method	:	other: Static Cell Multiplication Inhibition Test
Year	:	
GLP	:	no
Test substance	:	other TS: aqueous solution of formaldehyde (35%)
Remark	:	Test result: 2.5 mg/L formalin (35% solution) corresponds to 0.88 mg/L pure substance.

Test condition	:	Test vessel: Kapsenberg cultivation tubes (18 x 180 mm). Test volume: 10 ml Concentration of stock solution: not indicated Dilution: 1:2 Pre-treatment of test solution: neutralization if necessary Inoculum: cell density adjusted to TE/F = 20 (formalin turbidity equivalents at 578 nm) Number of test replicates: 3 Number of control replicates: 1 Illumination: constant artificial light (Osram L 40/30) Temperature: 27C Agitation: once daily Measurements: photometric determination of cell density 578 nm after 192 hr of exposure
Test substance	:	Test substance, formaldehyde, is a breakdown product of CMME.
Reliability	:	(2) valid with restrictions 2e: Meets generally accepted scientific standards, well-documented and acceptable for assessment

06.07.2004 (31)

Method	:	
Year	:	
GLP	:	
Test substance	:	other TS: aqueous solutions of hydrochloric acid
Remark	:	It is the resulting pH rather than the concentration of HCl that determines lethality toward aquatic life (Environment Canada, 1984). In general, a pH lower than 5 is lethal to most fish, although specialized aquatic flora and fauna may develop. Reference: Enviro Technical Information For Problem Spills (1984) Hydrogen Chloride/Hydrochloric Acid, Environment Canada Environmental Protection Service

06.07.2004

4.4 TOXICITY TO MICROORGANISMS E.G. BACTERIA

4.5.1 CHRONIC TOXICITY TO FISH

4.5.2 CHRONIC TOXICITY TO AQUATIC INVERTEBRATES

4.6.1 TOXICITY TO SEDIMENT DWELLING ORGANISMS

4.6.2 TOXICITY TO TERRESTRIAL PLANTS

4.6.3 TOXICITY TO SOIL DWELLING ORGANISMS

4.6.4 TOX. TO OTHER NON MAMM. TERR. SPECIES

4.7 BIOLOGICAL EFFECTS MONITORING

4.8 BIOTRANSFORMATION AND KINETICS

4.9 ADDITIONAL REMARKS

5.0 TOXICOKINETICS, METABOLISM AND DISTRIBUTION

5.1.1 ACUTE ORAL TOXICITY

Type	:	LD50
Value	:	
Species	:	rat
Strain	:	
Sex	:	
Number of animals	:	
Vehicle	:	
Doses	:	
Method	:	
Year	:	1948
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4
Method	:	Chloromethyl methyl ether was fed as a 10% solution in olive oil to rats.
Result	:	Animals survived at a single dose of 300 mg/kg whereas 1000 mg/kg caused death. No additional information supplied.
Reliability	:	(2) valid with restrictions 2e

02.08.2004 (32)

Type	:	LD50
Value	:	= 0.21 ml/kg bw
Species	:	rat
Strain	:	
Sex	:	
Number of animals	:	
Vehicle	:	
Doses	:	
Method	:	
Year	:	1969
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4
Method	:	Groups of 5 non-fasted Wistar rats, 4-5 weeks of age and 90-120 g in weight were used. Based upon mortalities during a 14-day observation period, the most probable LD50 value and its confidence intervals were estimated by the method of Thompson.
Remark	:	Based on the specific gravity of 1.0625, 0.21 ml/kg corresponds to 223 mg/kg.
Result	:	The single dose oral LD50 is 0.21 ml/kg with confidence intervals of 0.12-0.37. No additional information provided.
Reliability	:	(2) valid with restrictions 2e

22.07.2004 (33)

Type	:	LD50
Value	:	= 817 mg/kg bw
Species	:	rat
Strain	:	

Sex	:	
Number of animals	:	
Vehicle	:	
Doses	:	
Reliability	:	(4) not assignable 4b

22.07.2004 (34)

5.1.2 ACUTE INHALATION TOXICITY

Type	:	LC50
Value	:	
Species	:	rat
Strain	:	
Sex	:	
Number of animals	:	
Vehicle	:	
Doses	:	
Exposure time	:	
Method	:	
Year	:	1975
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4
Method	:	Groups of male Sprague-Dawley rats, approximately 8 weeks old, were exposed for a single 7-hour exposure to 12.5, 26, 42, 54, 70, 141 or 225 ppm chloromethyl methyl ether. Atmospheric analysis of CMME was conducted. Surviving animals were held for 14 days. All animals were necropsied and respiratory tract tissues saved for histopathological evaluation. Lung to body weight ratios were determined and compared to control values.
Remark	:	Mortality at 26 and 42 ppm is reportedly 110 and 225%, respectively. Obviously this is incorrect. It is not possible to tell what the correct values should be. Since moisture in air reacts very rapidly with chloromethyl methyl ether, the concentration to which these animals were exposed to is unknown.
Result	:	The 7-hour LC50 was 55 ppm. All animals died at 70 ppm and higher. Lungs of rats were congested and edematous with evidence of hemorrhage. These gross findings were present to a lesser extent even in animals that survived the 14-day post-exposure period. Acute necrotizing bronchitis was also observed. Based on a large colony control study, the average lung to body weight ratio was approximately 0.6 +/- 0.1 for rats. The authors have considered any values above mean plus 3 SD (0.9) for rats as elevated. Lung to body weight ratios were increased at concentrations of 26 ppm and higher. At 26 ppm, the lung to body weight ratio was 20% greater than control plus 3 SD. No additional information provided.
Reliability	:	(2) valid with restrictions 2e

02.08.2004 (35)

Type	:	LC50
Value	:	
Species	:	rat

Strain	:	
Sex	:	
Number of animals	:	
Vehicle	:	
Doses	:	
Exposure time	:	
Method	:	
Year	:	1948
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4
Method	:	Groups of 6 rats were exposed for 30, 60 or 240 minutes to vapor concentrations of 100, 200, 500, 1000, 2000, 5000 and 10,000 ppm.
Remark	:	Since moisture in air reacts very rapidly with chloromethyl methyl ether, the concentration to which these animals were exposed to is unknown.
Result	:	Lethality was observed in rats exposed to 2000 ppm and higher for 30 minutes or to 100 ppm and higher for 4 hours. Deaths resulting from vapor exposure are almost all delayed deaths occurring several days and even weeks after exposure. Most deaths were due to pneumonia. No additional information provided.
Reliability	:	(2) valid with restrictions 2e

02.08.2004 (32)

Type	:	LC50
Value	:	
Species	:	rat
Strain	:	
Sex	:	
Number of animals	:	
Vehicle	:	
Doses	:	
Exposure time	:	4 hour(s)
Method	:	
Year	:	1969
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4
Method	:	Groups of 6 rats were exposed to metered vapor concentrations of chloromethyl methyl ether for 4 hours. Metered vapor concentrations were generated by using various proportioning pumps to meter test material into the air stream prior to entering the chamber. Nominal concentration only was determined. Following the 4-hour exposure period, surviving animals were observed for 14 days.
Remark	:	Since moisture in air reacts very rapidly with chloromethyl methyl ether, the concentration to which these animals were exposed to is unknown.
Result	:	At a nominal concentration of 8 ppm, one of 6 rats died. At 16 ppm, all animals died during the 14-day post-exposure observation period.
Reliability	:	(2) valid with restrictions 2e

02.08.2004 (33)

Type	:	LC0
Value	:	
Species	:	mouse
Strain	:	Strain A
Sex	:	male
Number of animals	:	
Vehicle	:	

Doses	:	
Exposure time	:	6 hour(s)
Method	:	Groups of male mice were exposed for 6 hours to concentrations of CMME ranging from 14.6 - 100 ppm (nominal concentration). Animals were observed for a 14 day post-exposure interval.
Remark	:	Since moisture in air reacts very rapidly with chloromethyl methyl ether, the concentration to which these animals were exposed to is unknown.
Result	:	All animals survived a 6 hour exposure to a nominal concentration of 100 ppm. No further information provided.
Reliability	:	(2) valid with restrictions 2e

02.08.2004 (36)

Type	:	LC50
Value	:	
Species	:	hamster
Strain	:	
Sex	:	
Number of animals	:	
Vehicle	:	
Doses	:	
Exposure time	:	
Method	:	Groups of male Golden Syrian hamsters, approximately 6 weeks old, were exposed for a single 7-hour exposure to 12.5, 26, 42, 54, 70, 141 or 225 ppm chloromethyl methyl ether. Surviving animals were held for 14 days. All animals were necropsied and respiratory tract tissues saved for histopathological evaluation. Lung to body weight ratios were determined and compared to control values.
Result	:	The 7-hour LC50 was 65 ppm. All animals died at 225 ppm. Lungs of hamsters were congested and edematous with evidence of hemorrhage. These gross findings were present to a lesser extent even in animals that survived the 14-day post-exposure period. Acute necrotizing bronchitis was also observed. Based on a large colony control study, the average lung to body weight ratio was approximately 0.6 +/- 0.1 for hamsters. The authors have considered any values above mean plus 3 SD (0.8) for hamsters as elevated. Lung to body weight ratios were increased at concentrations of 26 ppm and higher. At 26 ppm, the lung to body weight ratio was 10% greater than control plus 3 SD. No additional information provided.
Reliability	:	(2) valid with restrictions 2e

09.06.2004 (35)

5.1.3 ACUTE DERMAL TOXICITY

Type	:	LD50
Value	:	= .28 ml/kg bw
Species	:	rabbit
Strain	:	New Zealand white
Sex	:	male
Number of animals	:	

Vehicle	:	
Doses	:	
Method	:	
Year	:	1969
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4
Method	:	For the dermal LD50 study, groups of 4 male albino New Zealand rabbits weighing 2.5 to 3.5 kg are used. The fur is removed from the entire trunk by clipping, and the dose is retained beneath an impervious plastic film. Animals are immobilized during the 24-hour contact period, after which the film is removed and the rabbits are observed for a 14-day observation period. Based upon mortalities during a 14-day observation period, the most probable LD50 value and its confidence intervals were estimated by the method of Thompson.
Remark	:	Based on the specific gravity of 1.0625, 0.28 ml/kg corresponds to 300 mg/kg.
Result	:	The dermal LD50 is 0.28 ml/kg with confidence intervals of 0.13 - 0.62).
Reliability	:	(2) valid with restrictions 2e

22.07.2004 (33)

5.1.4 ACUTE TOXICITY, OTHER ROUTES

5.2.1 SKIN IRRITATION

Species	:	rabbit
Concentration	:	
Exposure	:	
Exposure time	:	
Number of animals	:	
Vehicle	:	
PDII	:	
Result	:	
Classification	:	
Method	:	
Year	:	1948
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4
Method	:	One application of undiluted material was made to the rabbit ear. It was also applied to rabbit abdomen.
Result	:	Severe hyperemia, edema and denaturation was observed on the rabbit ear. Complete destruction of the abdominal wall was observed. No additional information provided.
Reliability	:	(2) valid with restrictions 2e

22.07.2004 (32)

Species	:	rabbit
Concentration	:	undiluted
Exposure	:	Open
Exposure time	:	24 hour(s)
Number of animals	:	
Vehicle	:	
PDII	:	
Result	:	

Classification	:	
Method	:	
Year	:	1969
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4
Method	:	Primary skin irritation on rabbits is recorded in a 10-grade ordinal series and is based upon the severest reaction that develops on the clipped skin of each of five albino rabbits within 24 hours of the uncovered application of 0.01 ml of undiluted sample.
Result	:	Application of 0.01 ml for 24 hour to uncovered rabbit abdomen resulted in necrosis (Grade Level 6). No additional information provided.
Reliability	:	(2) valid with restrictions 2e

22.07.2004 (33)

5.2.2 EYE IRRITATION

Species	:	rabbit
Concentration	:	
Dose	:	
Exposure time	:	
Comment	:	
Number of animals	:	
Vehicle	:	
Result	:	
Classification	:	
Method	:	
Year	:	1948
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4
Method	:	A drop of a 1% solution of chloromethyl ether in propylene glycol was placed in the rabbit eye.
Result	:	The material caused a severe irritation accompanied by extensive necrosis of the eye ball. No additional information supplied.
Reliability	:	(2) valid with restrictions 2e

22.07.2004 (32)

Species	:	rabbit
Concentration	:	undiluted
Dose	:	
Exposure time	:	
Comment	:	
Number of animals	:	
Vehicle	:	
Result	:	
Classification	:	
Method	:	
Year	:	1969
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4
Method	:	Eye irritation in rabbits is recorded in a 10-grade ordinal series based upon the degree of corneal necrosis that results from instillations of various

volumes and concentrations of test material.

Result : Instillation of 0.5 ml of a 1% solution in water or propylene glycol resulted in a severe burn (Grade Level 10).

No further information provided.

Reliability : (2) valid with restrictions
2e

22.07.2004 (33)

5.3 SENSITIZATION

5.4 REPEATED DOSE TOXICITY

Type :
Species : rat
Sex : male
Strain : Sprague-Dawley
Route of admin. : inhalation
Exposure period :
Frequency of treatm. :
Post exposure period :
Doses :
Control group :

Method : Thirty day studies on the effects of daily repeated inhalation of CMME were carried out at concentrations of 1 and 10 ppm with 25 rats in each group. Animals that died during the study or survived to the end of the study were subjected to a gross pathological examination. Lung to body weight ratios were calculated and the lungs of animals were fixed in formalin, stained with hematoxylin and eosin and examined histopathologically.

Remark : Although not explicitly stated, each exposure was expected to be 7 hours duration.

Result : At 10 ppm, the first rats died during the third exposure day and mortality increased progressively to 22 out of 25 animals by the 30th exposure day. The three surviving animals were killed two weeks following the last exposure day. A marked weight decrease was seen in the week immediately following the onset of the exposure, with some indication of recovery toward the end of exposure.

For the 9 animals that died within the first ten days of exposure, the average lung to body weight ratio was 1.6. For the 13 animals that died between exposures 11 and 22, the average lung to body weight ratio was 2.2. These are much higher than the control + 3SD value of 0.9. Regenerative hyperplasia of bronchial epithelium was found in 10 of the 25 animals and one animal was found to have squamous metaplasia.

At 1 ppm, one animal died on exposure day 16 and 22. Five of the rats surviving 30 exposures were killed at the end of the last exposure and five more were killed two weeks later. The remaining 13 rats were held for lifetime studies. The longest survivor lived for 648 days after the first exposure. Weight change in these animals was not significantly different from that of the controls. Four of the five animals sacrificed after 30 exposures had normal lungs, while one animal had slight bilateral hemorrhage. The animals retained for their life spans showed minimal mucosal effects with two showing regenerative hyperplasia, one squamous metaplasia of the the bronchial epithelium and one tracheal squamous metaplasia.

At 10 ppm, measurement for formaldehye revealed that approximately 50% of the chloromethyl methyl ether was degraded.

No further information provided.

Reliability : (2) valid with restrictions
2e

02.08.2004 (35)

5.5 GENETIC TOXICITY 'IN VITRO'

Type :
System of testing :
Test concentration :
Cycotoxic concentr. :
Metabolic activation :
Result :
Method :
Year :
GLP :
Test substance :

Result : Chloromethyl methyl ether was positive using genetically well characterized mutants of E coli and S typhimurium.

No additional information provided.

Reliability : (4) not assignable
4a

22.07.2004 (37)

Type : Bacterial reverse mutation assay
System of testing :
Test concentration :
Cycotoxic concentr. :
Metabolic activation :
Result :
Method :
Year :
GLP : no data
Test substance : other TS: described as CMME and BCME

Result : A table in IARC Supplement 6 lists chloromethyl methyl ether as positive without activation in the Salmonella mutagenicity assay.

Reliability : (4) not assignable
4e Document insufficient for assessment

22.07.2004 (38)

Type : DNA damage and repair assay
System of testing :
Test concentration :
Cycotoxic concentr. :
Metabolic activation :
Result : positive
Method :
Year : 1981
GLP :
Test substance : as prescribed by 1.1 - 1.4

Method : A chromosomal aberration test using human lymphocytes was conducted. In this study cells were cultured for a 4 hour period at 37C in humidified atmospheres containing 5% CO2 in presence or in absence of each dose

of CMME in sextuplicate samples. In addition, the effects of rat liver phenobarbital induced S-9 mix were also evaluated. Dose levels evaluated were 25, 5 and 10 ul/ml. To measure UDS, 10 mM hydroxyurea was added to each culture to block [3H]-TdR uptake. At the end of the culture period, 3H-TdR uptake by lymphocytes for SDS or for UDS was determined by liquid scintillation counting of 3H activity.

Result : A decrease in the uptake of [3H]-TdR was observed with CMME (Table 1).

Table 1

[3H]TdR uptake by human lymphocytes cultured for a 4 hour period

Compound	[3H]TdR uptake
Control	2661 +/- 57
CMME	856 +/- 9

Without S9 mix the uptake of 3H-TdR was decreased from control values with CMME and hydroxyurea (Table 2). With S9 the uptake of 3H-TdR was increased with CMME and hydroxyurea. Over the concentration range tested, the response was consistent from 2.5 to 10 ul/ml for both with and without S9 activation.

Table 2

[3H]TdR uptake by human lymphocytes cultured for a 4 hour period with hydroxyurea

	[3H]TdR uptake		
Compound	10 µl/ml	5 µl/ml	2.5 µl/ml
Without S9			
Control	715+/-24	715+/-24	715+/-24
CMME	313+/-26	278+/-13	346+/-20
With S9			
Control	612+/-26	612+/-26	612+/-26
CMME	1180+/-33	1320+/-57	1125+/-59

The authors ascribe the high UDS values for CMME could be due to bis(chloromethyl)ether.

Reliability : (2) valid with restrictions
2e

22.07.2004 (39)

Type : Chromosomal aberration test
System of testing :
Test concentration :
Cycotoxic concentr. :
Metabolic activation : without
Result : positive
Method : other: essentially follows OECD 473
Year : 1996
GLP : no data
Test substance : as prescribed by 1.1 - 1.4

Remark : No addtional information provided.
Result : CMME was positive in CHL cells at 0.015 mg/ml 24 hours after treatment without metabolic activation.
Reliability : (3) invalid
3a

22.07.2004 (40)

Type	:	other: adenovirus transformation using hamster cells
System of testing	:	
Test concentration	:	
Cycotoxic concentr.	:	
Metabolic activation	:	
Result	:	positive
Method	:	
Year	:	1980
GLP	:	
Test substance	:	no data

Method : Primary cell cultures of Syrian hamster embryo cells (HEC) were prepared. Following 3 to 4 days of incubation at 37C, each of two dishes of cells were treated for 2 or 18 hours with at least 5 dilutions of test chemical, rinsed and inoculated with SA7. After 3 hours of virus absorption, the cells were removed from the dish, centrifuged and resuspended in complete medium. Cells were maintained for 21-25 days at which point they were formalin fixed and stained with Giemsa stain. The SA7-transformed foci were easily identified by their unique morphology.

Result : A positive response was observed with a 10% concentration.

No additional information provided.

Reliability : (3) invalid
3a

22.07.2004 (41)

5.6 GENETIC TOXICITY 'IN VIVO'

Type	:	Micronucleus assay
Species	:	mouse
Sex	:	
Strain	:	
Route of admin.	:	
Exposure period	:	
Doses	:	
Result	:	ambiguous
Method	:	OECD Guide-line 474 "Genetic Toxicology: Micronucleus Test"
Year	:	1997
GLP	:	no data
Test substance	:	as prescribed by 1.1 - 1.4

Method : Groups of 5 male mice were treated by ip injection once with CMME at dose levels of 0, 25, 50 and 100 mg/kg. Samples of bone marrow or pheripheral blood were evaluated.

Result : Inconclusive results were obtained with CMME (Table 3). Although some samples showed statistically significant positive responses, the results were considered inconclusive due to the poor reproducibility.

Table 1
Summary of micronucleus assay results for
chloromethylmethyl ether

strain	tissue	dose (mg/kg)	Percent MNPCE or MNRET 24 hr	48 hr
CD-1	pb	0	0.18+/-0.09	
		25	0.22+/-0.08	0.22+/-0.14
		50	0.38+/-0.12	0.28+/-0.14
		100	0.55+/-0.13	0.26+/-0.25
CD-1	bm	0	0.36+/-0.17	
		25	0.22+/-0.26	0.34+/-0.21
		50	0.20+/-0.14	0.14+/-0.05
		100	0.54+/-0.39	0.40+/-0.25

pb - peripheral blood
bm - bone marrow

Table 2
Summary of micronucleus assay results for
chloromethylmethyl ether

strain	tissue	dose (mg/kg)	Percent MNPCE or MNRET 24 hr	48 hr
CD-1	pb	0	0.14+/-0.13	
		25	0.25+/-0.10	0.28+/-0.17
		50	0.52+/-0.24	0.40+/-0.25
		100	1.04+/-0.73	0.34+/-0.23
CD-1	bm	0	0.16+/-0.11	
		25		0.30+/-0.16
		50	0.13+/-0.05	0.32+/-0.15
		100	0.50+/-0.08	0.38+/-0.23

pb - peripheral blood
bm - bone marrow

Table 3
Summary of micronucleus assay results for
chloromethylmethyl ether in peripheral blood of ICR mice

dose (mg/kg)	Percent MNPCE or MNRET 0	24	48	72
25	0.24+/-0.16	0.33+/-0.18	0.23+/-0.03	0.25+/-0.09
50	0.24+/-0.13	0.29+/-0.09	0.33+/-0.17	0.19+/-0.05
100	0.35+/-0.09	0.36+/-0.16	0.35+/-0.00	0.40+/-0.09

Test substance : Authors used reagent-grade CMME with a purity of 95.7%.
Reliability : (2) valid with restrictions
2e

22.07.2004 (42)

5.7 CARCINOGENICITY

Species : rat
Sex : male
Strain : Sprague-Dawley
Route of admin. : inhalation
Exposure period :
Frequency of treatm. :

Post exposure period	:	
Doses	:	1 ppm
Result	:	
Control group	:	yes, concurrent no treatment
Method	:	
Year	:	1975
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4

Method : Groups of 74 male Sprague-Dawley rats were exposed to 0 or 1 ppm chloromethyl methyl ether for 6 hours/day, 5 days/week for a lifetime. By the end of the study, rats had received as many as 565 exposures over a period of 852 days. At the time of necropsy, lungs of animals were removed and filled with 10% neutral buffered formalin. Lungs were stained with hematoxylin-eosin and examined histopathologically.

Result : Mortality and body weight gain were comparable between rats from the control and 1 ppm groups. Histologic changes in the trachea and bronchi were observed in rats exposed to 1 ppm. Treatment-related changes included tracheal squamous metaplasia and bronchial hyperplasia. A squamous cell carcinoma of the lung was discovered in an animal dying at 700 days. An animal dying at 790 days was found to have esthesioneuroepithelioma of olfactory epithelium.

No additional information provided.

Reliability : (2) valid with restrictions
2e

22.07.2004 (43)

Species	:	hamster
Sex	:	male
Strain	:	
Route of admin.	:	inhalation
Exposure period	:	
Frequency of treatm.	:	
Post exposure period	:	
Doses	:	
Result	:	
Control group	:	
Method	:	
Year	:	1975
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4

Method : Groups of 90 male Golden Syrian hamsters were exposed to 0 or 1 ppm chloromethyl methyl ether for 6 hours/day, 5 days/week for a lifetime. By the end of the study, hamsters had received as many as 565 exposures over a period of 852 days. At the time of necropsy, lungs of animals were removed and filled with 10% neutral buffered formalin. Lungs were stained with hematoxylin-eosin and examined histopathologically.

Result : Mortality and body weight gain were comparable between rats from the control and 1 ppm groups. Histologic changes were observed in the lung of hamsters. Nine animals had bronchoalveolar metaplasia and ten were seen with atypical alveolar cells. Atypical alveolar cells were indicated by the presence of large, bizarre, pleomorphic, angular and hyperchromatic nuclei. An adenocarcinoma of the lung was found in an animal sacrificed at 134 days after 90 exposures. Additionally, a squamous papilloma of the trachea was seen in an exposed animal that died after 683 days.

No additional information provided.

Reliability : (2) valid with restrictions
2e

02.08.2004 (43)

Species	:	mouse
Sex	:	male
Strain	:	Strain A
Route of admin.	:	inhalation
Exposure period	:	6 hrs/day, 5 days/week for 21 weeks
Frequency of treatm.	:	
Post exposure period	:	
Doses	:	2 ppm (nominal)
Result	:	
Control group	:	yes
Method	:	
Year	:	1971
GLP	:	
Test substance	:	as prescribed by 1.1 - 1.4

Method : The vapor atmosphere of CMME was obtained by metering the liquid compound with a precision syringe into the air stream entering the chamber to obtain the desired nominal concentration. The analytical concentration was not determined. A group of 50 treated animals was exposed for 6 hrs/day, 5 days/week for 101 days in 21 weeks. A group of 50 control animals was exposed to room air for 6 hrs/day, 5 days/week for 130 days in 28 weeks. During the in-life portion of the study, the animals were observed and weighed. All animals which died during the exposure period were examined. At the termination of the studies, all survivors were killed. Lung specimens from all animals were preserved in formaldehyde solution and examined for tumors. The number of tumors in the lungs was counted and the ratios of the average number of tumors per animal between the treated and the control group was calculated. A ratio of two or greater is considered to be a positive response.

Remark : Since moisture in air reacts very rapidly with chloromethyl methyl ether, the concentration to which these animals were exposed to is unknown.

Result : There were no effects on mean body weight and demeanor of animals exposed to CMME. Four animals died of unknown causes. Gross necropsies of the dead and the survivors revealed lung abnormalities in 37 animals. Of the 37 animals, 25 also had lung tumors. The average number of tumors per tumor-bearing animal was 3.1 and the mean number of tumors for the group was 1.53.

Test substance : Test substance defined as industrial grade sample. No further information provided.

Reliability : (2) valid with restrictions
2e

02.08.2004 (36)

Species	:	mouse
Sex	:	male/female
Strain	:	SKH/HR1
Route of admin.	:	
Exposure period	:	
Frequency of treatm.	:	
Post exposure period	:	
Doses	:	
Result	:	
Control group	:	
Method	:	
Year	:	1969
GLP	:	
Test substance	:	as prescribed by 1.1 - 1.4

Method : ICR Swiss mice 24-72 hours old and weighing an average of 2 g, received a single subcutaneous injection of the vehicle or experimental chemical. The maximum tolerated dose (85% survival 30 days post-treatment) was

determined for each compound in a preliminary dose-range study.

Industrial grade bis(chloromethyl)ether and chloromethyl methyl ether were used. The concentration of BCME in CMME was 0.3% at the beginning of the study and 2.6% at the end of the study. Urethan (ethyl carbamate) was used as a positive control. The vehicle control animals received 0.05 ml peanut oil.

Animals were weaned at approximately 30 days of age and housed individually in hanging wire cages. They were observed daily for mortality and weekly for gross effects. Body weights were recorded monthly. Animals which died during the study were necropsied, and all animals were sacrificed 6 months after compound administration.

Lungs were fixed in Tellyesniczky's fluid. The 5 lobes were examined individually with a dissecting microscope, and the lung adenomas were identified and counted. Representative adenomas were sectioned and examined for histopathologic confirmation and characterization of the lesions. Other grossly abnormal tissues were fixed in 10% formalin and examined.

Result : The number of animals with adenomas was increased slightly in males and females receiving CMME.

Table 1

Compound	Dose/kg	Number	Sex	Number animals w adenomas	Total number of adenomas
Peanut oil	25 ml	20	F	5	5
		30	M	2	2
Urethan	1500 mg	25	F	25	454
		25	M	25	402
BCME	12.5 ul	50	F	20	23
		50	M	25	41
CMME	125 ul	48	F	8	9
		51	M	9	12

Reliability : (2) valid with restrictions
2e

02.08.2004 (44)

Species : mouse
Sex :
Strain : Swiss
Route of admin. :
Exposure period :
Frequency of treatm. :
Post exposure period :
Doses :
Result :
Control group :
Method :
Year : 1969
GLP : no
Test substance : as prescribed by 1.1 - 1.4

Method : Groups of 20 mice were treated with benzo[a]pyrene (B[a]P), CMME or nothing as initiators and acetone, phorbol esters (PE), CMME or nothing as promotors. For the initiation phase, mice were treated once with doses as

detailed in Table 1. For the promotion phase, mice were treated three times/week beginning 14 days after the initiation phase. Treatment of all animals was discontinued after 325 days but the animals were maintained and observed for the duration of the experiment, 540 days.

Result : Chloromethyl methyl ether applied on mouse skin as a 2% solution in benzene, 0.1 ml/application, i.e., 2 mg of CMME/application, was inactive as a carcinogen.

It proved to be an initiating agent at both 1000 and 100 ug doses with phorbol ester as the promotor, with 5/20 and 7/20 animals, respectively, bearing papillomas and 1/20 and 4/20, respectively, bearing squamous carcinomas (Table 1). The time to first tumor was 140 days with the 1000 ug dose of CMME as initiator whereas the 100 ug dose resulted in a latent period of 259 days.

Table 1
Incidence of skin tumors following various applications of CMME

Initiator	Dose mg/ 0.1ml	Promotor	Dose mg/ 0.1ml	Number of papillomas	Number of squamous carcinomas
None		None		0	0
None		CMME	2.0	0	0
CMME	0.1	None		0	0
CMME	1.0	None		0	0
CMME	1.0	Acetone	0.1	0	0
CMME	0.1	PE	0.025	7	4
CMME	1.0	PE	0.025	5	1
B[a]P	0.15	CMME	2.0	1	0

Reliability : (2) valid with restrictions
2e

22.07.2004 (45)

Species :
Sex :
Strain :
Route of admin. :
Exposure period :
Frequency of treatm. :
Post exposure period :
Doses :
Result :
Control group :
Method :
Year :
GLP :
Test substance :

Method : Groups of 30 female Swiss mice received subcutaneous injections once/week on the left flank for their lifetime. The vehicle used was purified paraffin oil. Animals were weighed regularly and examined once a month for palpable masses at the injection site. Mice observed with tumors for two months or moribund were necropsied. Routine sections were obtained of the injection site as well as any other gross abnormalities.

Result : Ten sarcomas were observed at the injection site. There was no significant incidence of tumors at other sites. The first tumor was observed 308 days after the first dose. The median survival time was 496 days.

No additional information provided.

Reliability : (3) invalid
3b

22.07.2004 (19)

5.8.1 TOXICITY TO FERTILITY

Test substance : Test substance, formaldehyde, is a breakdown product of CMME.
Conclusion : SIAR concludes no effects on reproductive organs were observed after chronic administration of formaldehyde to male and female rats. Amounts of formadehyde which produce marked toxic effects at the portal of entry, do not lead to an appreciable systemic dose and thus do not produce systemic toxicity.
Reliability : (2) valid with restrictions
2e Meets generally accepted scientific standards, well-documented and acceptable for assessment

10.08.2004

Test substance : Test substance, hydrogen chloride, is a breakdown product of CMME.
Conclusion : SIAR concludes although no reliable studies have been reported regarding toxicity to reproduction after oral, dermal or inhalation exposure to hydrogen chloride/hydrochloric acid, because protons and chloride ions are normal constituents in the body fluid of animal species, low concentrations of hydrogen chloride gas/mist or solution do not seem to cause adverse effects to animals. In addition, no effects on the gonads were observed in a good quality 90 day inhalation study up to 50 ppm.
Reliability : (2) valid with restrictions
2e Meets generally accepted scientific standards, well-documented and acceptable for assessment

10.08.2004

Method : A two-generation reproductive study using Sprague-Dawley rats (specific pathogen free) was performed by the New Energy Development Organization (NEDO), following the Organization for Economic Cooperation (OECD) Guidelines. This study does not give detailed animal results; only conclusions are presented. All rats were exposed to 0 (controls), 13.3, 133 or 1330 mg/m3 (0, 10, 100 and 1000 ppm), with 30 males and 30 females in each group. The parent (Fo) was exposed from age 8 weeks through mating, birth and weaning of the F1 generation. The F1 generation was subsequently continuously exposed through mating, birth and weaning of the F2 generation. The F2 generation was similarly exposed to 21 days of age.
Result : In the Fo generation, male rats at the high-dose level of 1330 mg/m3 (1000 ppm) showed inhibition of body weight gain after 7 weeks of exposure. Similar but not significant differences were observed in the female rats. Food consumption was significantly decreased in male and female rats at the high dose. The general condition of the animals remained unchanged. There was no effect on the sexual cycle or reproductive capacity. In the F1 generation there were no changes in general condition, body weight or food or water consumption. There was an early occurrence of the testis descending. Autopsy in rats 8 weeks of age revealed significantly reduced brain weight in males and females in the high-dose group; at 16 weeks of age male rats had reduced brain weight, as did female rats at 24 weeks. Histopathology was normal. In the F2 generation no abnormalities were found in the general condition, body weight or food and water consumption. In postnatal morphological differentiation, a significant slightly early testis descent occurred in high-dose male rats. Organ weight measurement at autopsy of 8-week-old rats showed significantly decreased organ weights of the brain, hypophysis and thymus in male and female rats in the high-dose group. In the low-dose group, 13.3 mg/m3 (10 ppm), and middle-

dose group, 133 mg/m3 (100 ppm), there were no methanol effects noted. Therefore the No-Observed-Adverse-Effect-Level (NOAEL) for this study is 13.3 mg/m3.

Test substance : Test substance, methanol, is a breakdown product of CMME.
Reliability : (4) not assignable
4b: Secondary literature

16.08.2004 (46)

5.8.2 DEVELOPMENTAL TOXICITY/TERATOGENICITY

Species	:	rat
Sex	:	female
Strain	:	Sprague-Dawley
Route of admin.	:	inhalation
Exposure period	:	6 hrs/day
Frequency of treatm.	:	days 6-15 of gestation
Duration of test	:	daily
Doses	:	ca. 0.002, 0.006 and 0.012 mg/L (2, 5 and 10 ppm)
Control group	:	yes
NOAEL maternal tox.	:	= .006 mg/l
NOAEL teratogen.	:	= .012 mg/l
Method	:	other: no data
Year	:	
GLP	:	no data
Test substance	:	other TS: no data on purity of formaldehyde

Method : The study consisted of expsoing groups of 25 mated Sprague-Dawley rats by the whole-body exposure technique for 6 hrs/day, wiht formaldehyde at dosages of 2, 5 or 10 ppm from day 6 to day 15 of gestation. Two control groups were included in the study; one was handled in an identical manner to the formaldehyde-treated groups except that it was treated with air, and the other was maintained in the animal room throughout the study. The females used for the study were 13 weeks of age and weighed between 221 and 277g.

The group mean +/- SD live liter size, corporus luteum count, number of implants, and number of resorptions were calculated. The individual and group litter mean +/- SD for the preimplantation and postimplantation losses were calculated. The litter sex ratio was calculated for statistical analysis and the group sex ratio presented. Statistical analysis of these parameters was performed using the Mann-Whitney U test.

The teratogenic effects of whole-body inhalation exposure to formaldehyde was studied in groups of 25 rats. The measured concentrations of the test substance were 0.01, 1.88, 4.88 and 9.45 ppm in the air-control, 2, 5 and 10 ppm groups, respectively.

Remark : Robust summary essentially copied from UNEP dossier (2 Sept 2003) for formaldehyde.

Result : The pregnancy rate in all groups was at least 80%. In the highest dose group, a significant decrease in maternal feed consumption and body weight gain was observed. Pregnancy parameters (numbers of corpora lutea, implantation sites, live fetuses, dead fetuses and resorptions, preimplantation and postimplantation losses, fetal weights and sex ratios) were unaffected. No evidence of maternal toxicity was found in the other groups.

The overall incidences of litters and fetuses wiht major malformations, minor external and visceral anomalies andminor skeletal anomalies were similar. At the 10 and 5 ppm levels, an apparently significant dose-related decrease in ossification was detected in the bones of the pelvic girdle.

However, this alteration was only significant when compared with air-controls, but not when compared with room -controls. Thus, according to the authors, this finding was associated with larger litter sizes being accompanied by decreased fetal weights. According to the authors, neither this finding nor other parameters assessed demonstrated any adverse effect on the conceptus due to formaldehyde exposure under the conditions used in this study.

Test substance : Test substance, formaldehyde, is a breakdown product of CMME.
Reliability : (2) valid with restrictions
2e Meets generally accepted scientific standards, well-documented and acceptable for assessment

10.08.2004 (47)

Species : rat
Sex : female
Strain : Sprague-Dawley
Route of admin. : inhalation
Exposure period : 6 hours/day
Frequency of treatm. : days 6-20 of gestation
Duration of test :
Doses : 0.006, 0.012, 0.025 and 0.05 mg/L (5, 10, 20 and 40 ppm)
Control group : yes, concurrent no treatment
NOAEL maternal tox. : = 20 ppm
NOAEL teratogen. : = 40 - ppm
Method : other: no data
Year :
GLP : no data
Test substance : other TS: 37% aqueous solution of formaldehyde, containing 10% methanol. No data on purity of the compound

Method : Groups of 25 mated female rats were whole body exposed. The atmosphere concentrations were sampled periodically and samples were analyzed spectrophotometrically after derivatization with chromotropic acid.

Maternal toxicity was evaluated by clinical examination and body weight determination. Implantation and resorption sites were determined in the uteri.

Fetal examination comprised differentiation of live and dead fetuses, fetal weights and sex, external malformation and skeletal and soft tissue malformations after appropriate fixation.

Remark : Robust summary essentially copied from UNEP dossier (2 Sept 2003) for formaldehyde.

From the data on repeated dose inhalation toxicity it is inferred, that at the concentration of 10 and 20 ppm maternal toxicity was present in form of nasal irritation and epithelial damage, which impose considerable stress on the animals and represent maternal toxicity in addition to the observed retarded body weight development.

Thus the slight fetotoxicity found at 20 ppm is considered to be related to maternal toxicity.

Result : Maternal toxicity was indicated by a significantly reduced body weight gain at the highest dose level (0.05 mg/L, 40 ppm).

The pregnancy rate was at least 21/25 (84%).

No substance-related effect on lethality of embryo or fetus was recorded. No significant external, visceral or skeletal anomalies were observed in fetuses of any groups. At the hgih and high intermediate concentration reduction of fetal body weight was observed (ca. 5% in males at 0.025 mg/L, 20 ppm and 20% at 0.05 mg/L, 40 ppm) as compared to air control.

According to the authors, these results suggest that the test substance had a slightly fetotoxic effect at concentrations of 20 ppm and more. Neither embryolethal nor teratogenic effects were observed.

Test substance : Test substance, formaldehyde, is a breakdown product of CMME.
Reliability : (2) valid with restrictions
2e Meets generally accepted scientific standards, well documented and acceptable for assessment

10.08.2004 (48)

Method :
Year :
GLP :
Test substance : other TS: hydrogen chloride

Remark : SIAR conclusions essentially copied from draft OECD documents for hydrogen chloride which can be found at http://www.oecd.org/dataoecd/57/35/31033889.pdf

No reliable studies have been reported regarding toxicity to reproduction and development in animals after oral, dermal or inhalation exposure to hydrogen chloride/hydrochloric acid. Because protons and chloride ions are normal constituents in the body fluid of animal species, low concentrations of hydrogen chloride gas/mist or solution do not seem to cause adverse effects to animals. In fact the cells of gastric glands secrete hydrochloric acid into the cavity of the stomach and orally administered sulfuric acid, which results in pH changes as well, did not cause developmental toxicity to laboratory animals. These facts indicate that hydrogen chloride/hydrochloric acid is not expected to effect developmental toxicity. In addition, no effects on the gonads were observed in a good quality 90-day inhalation study up to 50 ppm.

Test substance : Test substance, hydrogen chloride, is a breakdown product of CMME.
Reliability : (2) valid with restrictions
2e Meets generally accepted scientific standards, well-documented and acceptable for assessment

10.08.2004

Species : rat
Sex : female
Strain : Sprague-Dawley
Route of admin. : inhalation
Exposure period : 7 hours/day
Frequency of treatm. : days 1-19 of gestation (days 7-15 for the high concentration group)
Duration of test : 19 days
Doses : 5000, 10,000 and 20,000 ppm
Control group : yes, concurrent no treatment
Method : other: essentially follows OEcd 414
Year : 1985
GLP : no data
Test substance : other TS: >99% methanol

Method : Groups of 13-15 bred female rats were exposed to 0, 5000, 10,000 or 20,000 ppm methanol for 7 hours/day on days 1-19 of gestation. Animals in the 20,000 ppm group were only exposed on days 7-15 of gestation. Dams were sacrificed on gestation day 20 (sperm = day 0). One half of the fetuses were examined using the Wilson technique for visceral defects and the other half were examined for skeletal defects.

Result : At the highest concentration, 20,000 ppm, dams had slightly unsteady gait after the initial days of exposure, but feed intake, water consumption and body weights were not significantly affected. Exposure of pregnant rats to methanol had no effect on the numbers of corpora lutea or implantations or the percentage of dead or resorbed fetuses. However, at the two higher concentrations, methanol depressed fetal weights in a dose-related manner

(Attachment 1). There was also a dose-related increase in the incidence of malformations after methanol exposure (Attachment 1).

In conclusion, methanol was definitely teratogenic at 20,000 ppm, possibly teratogenic at 10,000 ppm but not teratogenic at 5000 ppm.

Test substance : Test substance, methanol, is a breakdown product of CMME.
Attached document : methanol developmental tox.pdf

TABLE 2

OBSERVATIONS MADE AT THE TIME OF CESAREAN SECTION OF RATS EXPOSED TO METHANOL AND ETHANOL[a]

	MECO	10ME	20ME	ETCO	10ET	16ET	EMCO	5ME	20ET
No. pregnant/No. bred	15/15	15/15	15/16	15/15	15/15	15/16	15/15	13/14	14/16
$\bar{x}$ Corpova lutea/dam ± SD	15 ± 1	17 ± 1	—[b]	15 ± 2	14 ± 1	16 ± 1	14 ± 3	16 ± 2	15 ± 2
$\bar{x}$ Implants/dam ± SD	15 ± 1	16 ± 1	14 ± 1	15 ± 2	14 ± 1	16 ± 1	14 ± 3	15 ± 1	14 ± 2
Percentage of implants resorbed	8	5	10	7	4	7	6	4	6
Sex ratio (F:M)	53:47	52:48	58:42	47:53	54:46	59:41	51:49	56:44	55:45
$\bar{x}$ Fetal weights ± SD (g)									
Female	3.15 ± 0.32	2.93 ± 0.26*	2.76 ± 0.47*	3.10 ± 0.36	3.10 ± 0.57	3.09 ± 0.43	2.99 ± 0.32	3.19 ± 0.24	2.94 ± 0.25
Male	3.34 ± 0.36	3.12 ± 0.30*	2.82 ± 0.56*	3.33 ± 0.31	3.26 ± 0.55	3.18 ± 0.39	3.16 ± 0.29	3.30 ± 0.24	3.06 ± 0.28

[a] Rats were exposed 7 hr/day throughout gestation. MECO = methanol controls; 10ME = 10,000 ppm methanol; 20ME = 20,000 ppm methanol (exposure was for Gestation Days 7–15); ETCO = ethanol controls; 10ET = 10,000 ppm ethanol; 16ET = 16,000 ppm ethanol; EMCO = ethanol, methanol controls; 5ME = 5000 ppm methanol; and 20ET = 20,000 ppm ethanol. (The EMCO group was added subsequent to our initial evaluation of methanol and ethanol; it was the comparison group for 5ME and 20ET.)
[b] Information not collected.
* Significantly different from appropriate control group at $p \leq 0.05$.

TABLE 3

SKELETAL MALFORMATIONS IN RATS AFTER PRENATAL EXPOSURE TO METHANOL AND ETHANOL[a]

	MECO	10ME	20ME	ETCO	10ET	16ET	EMCO	5ME	20ET
No. litters (fetuses) observed	15 (98)	15 (115)	15 (92)	15 (99)	15 (100)	15 (107)	15 (90)	13 (90)	14 (92)
No. litters (fetuses) affected									
Cranial	0	0			0	0	0	0	0
Abnormal exoccipital			2 (3)	0					
Abnormal zygomatic			1 (1)	0					
Abnormal nasal			0	1 (1)					
Shortened maxilla			0	1 (1)					
Split basisphenoid			0	1 (1)					
Vertebral	0				0	0	0	0	
Scoliosis		0	1 (1)	0					0
Decreased thoracic vert.		0	1 (1)	0					0
Fused thoracic centra		0	2 (2)	1 (1)					0
Decreased lumbar vert.		1 (1)	1 (1)	0					0
Fused lumbar centra		0	2 (2)	0					0
Fused cervical arches		0	0	1 (1)					0
Lordosis		0	0	0					1 (1)
Ribs	0				0		0		
Rudimentary cervical		2 (2)	12 (39)	1 (1)		2 (2)		0	2 (2)
Extra cervical		0	10 (35)	0		0		0	0
Wavy/fused		0	3 (3)	2 (2)		0		0	2 (3)
Missing		0	7 (7)	0		1 (1)		1 (1)	0
Total malformations, litters (fetuses)	0	2 (2)	14 (72)	4 (4)	0	2 (3)	0	1 (1)	4 (5)

[a] Rats were exposed 7 hr/day throughout gestation. MECO = methanol controls; 10ME = 10,000 ppm methanol; 20ME = 20,000 ppm methanol (exposure was for gestation days 7–15); ETCO = ethanol controls; 10ET = 10,000 ppm ethanol; 16 ET = 16,000 ppm ethanol; EMCO = ethanol, methanol controls; 5ME = 5000 ppm methanol; and 20ET = 20,000 ppm ethanol. (The EMCO group was added subsequent to our initial evaluation of methanol and ethanol; it was the comparison group for 5ME and 20ET.)

TABLE 4

VISCERAL MALFORMATIONS IN RATS AFTER PRENATAL EXPOSURE TO METHANOL AND ETHANOL[a]

	MECO	10ME	20ME	ETCO	10ET	16ET	EMCO	5ME	20ET
No. litters (fetuses) observed	15 (107)	15 (107)	15 (96)	15 (107)	15 (106)	15 (114)	15 (99)	13 (90)	14 (97)
No. litters (fetuses) affected									
Cardiovascular	0			0	0		0	0	0
Right aortic arch		1 (1)	1 (2)			1 (1)			
Right ductus arteriosis		0	1 (1)			1 (1)			
Ventricular septal defect		1 (1)	3 (3)			0			
Missing innominate		0	2 (2)			0			
Abnormal subclavian		1 (1)	1 (1)			0			
Right azygos vein		0	1 (1)			0			
Aortic coarctation		1 (1)	0			0			
Urinary	0			0		0			
Hydroureter		1 (1)	3 (4)		0			0	0
Hydronephrosis		2 (2)	2 (4)		2 (2)			1 (2)	4 (4)
Ectopic kidney		0	1 (1)		0			0	0
Bladder hypoplasia		0	5 (10)		0			0	0
Bladder agenesis		0	1 (2)		0			0	0
Mis-shaped kidney		0	1 (1)		0			0	0
Eye	0				0	0	0	0	0
Microopthalmia		0	2 (2)	1 (1)					
Anopthalmia		1 (1)	0	1 (1)					
Abnormal/missing optic nerve		1 (1)	0	1 (1)					
Ablepharia		0	3 (3)	0					
Abnormal lens		0	2 (2)	0					
Brain	0			0	0	0	0	0	0
Hydrocephalus		2 (4)	2 (2)						
Exencephaly		0	3 (4)						
Encephalocele		0	2 (3)						
Total malformations, litters (fetuses)	0	2 (2)	7 (15)	1 (1)	2 (2)	1 (1)	0	1 (2)	4 (4)

[a] Rats were exposed 7 hr/day throughout gestation. MECO = methanol controls; 10ME = 10,000 ppm methanol; 20ME = 20,000 ppm methanol (exposure was for Gestation Days 7–15); ETCO = ethanol controls; 10ET = 10,000 ppm ethanol; 16ET = 16,000 ppm ethanol; EMCO = ethanol, methanol controls; 5ME = 5000 ppm methanol; and 20ET = 20,000 ppm ethanol. (The EMCO group was added subsequent to our initial evaluation of methanol and ethanol; it was the comparison group for 5ME and 20ET.)

TABLE 5

SUMMARY OF MALFORMATIONS AND VARIATIONS IN RATS AFTER PRENATAL EXPOSURE TO METHANOL AND ETHANOL[a]

	MECO	10ME	20ME	ETCO	10ET	16ET	EMCO	5ME	20ET
No. litters (fetuses) examined	15 (205)	15 (222)	15 (188)	15 (206)	15 (206)	15 (221)	15 (189)	13 (180)	14 (189)
No. litters/% fetuses with skeletal malformations	0	2/2	14*/79	3/3	0	2/3	0	1/1	4/5
No. litters/% fetuses with visceral malformations	0	5/8	10*/29	1/1	2/2	1/1	0	1/3	4/5
No. litters/% fetuses with skeletal variations	8/12	11/24	14/69	13/30	15/38	14/45	14/42	12/27	14/47
No. litters/% fetuses with visceral variations	11/21	13/26	12/26	10/16	7/10	7/15	6/8	7/11	8/9
No. litters with abnormal fetuses[b]	0	7	14	4	2	2	0	2	7
% of Litters with abnormal fetuses[b]	0	47	93*	27	13	13	0	15	50
% of Normal fetuses	100	96	46*	98	99	98	99	98	95

[a] Rats were exposed 7 hr/day throughout gestation. MECO = methanol controls; 10ME = 10,000 ppm methanol; 20ME = 20,000 ppm methanol (exposure was for Gestation Days 7–15), ETCO = ethanol controls; 10ET = 10,000 ppm ethanol; 16ET = 16,000 ppm ethanol; EMCO = ethanol; methanol controls; 5ME = 5000 ppm methanol; and 20ET = 20,000 ppm ethanol. (The EMCO group was added subsequent to our initial evaluation of methanol and ethanol; it was the comparison group for 5ME and 20ET.)
[b] Having skeletal or visceral malformations.
* Significantly different from the appropriate control group $p < 0.05$.

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Reliability : (2) valid with restrictions
2e Meets generally accepted scientific standards, well-documented and acceptable for assessment.

10.08.2004 (49)

5.8.3 TOXICITY TO REPRODUCTION, OTHER STUDIES

Type : other
In vitro/in vivo :
Species :
Sex :
Strain :
Route of admin. :
Exposure period :
Frequency of treatm. :
Duration of test :
Doses :
Control group :

Remark : CMME is a closed system intermediate with very low exposure guideline values. EPA guidance is that reproduction toxicity studies are unnecessary for closed system intermediates.

06.07.2004

5.9 SPECIFIC INVESTIGATIONS

5.10 EXPOSURE EXPERIENCE

Method : A historical prospective epidemiology study was conducted on workers exposed to chloromethyl methyl ether (CMME). Production workers employed at any time between 1948 and 1972 were followed. The total cohort of 2285 consisted of 669 men believed to have had exposure to CMME plus a non-exposed group of 1616 men from production operations in other sections of the same plant. Supervisory personnel associated with manufacture and use of CMME during the study period ranked the exposure of all job classifications at risk, whether or not a particular job was directly involved in the CMME operations. Any particular job was rated on a severity scale of 0 to 6. The total exposure time for each member of the cohort was also determined.

The Maher paper followed this cohort to Dec 31, 1981, an additional 9

years. In addition, short-term employees previously excluded from the cohort have been added.

Remark : epidemiology study
Studies by Figueroa et al., (1973), Weiss and Boucot (1975), DeFonso and Kelton (1976), Pasternack, Shore and Albert (1977) and Collingwood, Pasternack and Shore (1987) were conducted on part of the same population.

Result : Results based on DeFonso paper:
The 669 men employed in the CMME industry had a combined 11,087 man-years. A total of 19 lung cancer cases were observed when 5.0 were expected based on rates in unexposed production workers. This resulted in an SMR for the exposed population of 3.8.

For the entire exposure group, there was also significantly higher relative risks for workers in the intermediate exposure level with a total exposure time of 5 or more years and in the high exposure level with a total exposure time of 1 or more years.

Results based on Maher paper:
Of the 737 men employed in the CMME industry, there were 32 observed cases of respiratory tract cancer vs 11.5 expected for an SME of 2.79.
Results based on Maher paper: This is a later follow-up study to the DeFonso paper and follows essentially the same group of workers through 1981. Short-term employees previously excluded from the cohort have been added, and follow-up has been extended an additional 9 years. Thus the population was 737 exposed and 2120 unexposed workers. Mortality from cancer of the respiratory was 2.79 fold greater than expected (32 observed; 11.5 expected).

Reliability : (2) valid with restrictions
2e

22.07.2004 (50) (51)

Method : A prospective study of 125 chemical workers was carried out for 10 years (Dec 31, 1962 to Dec 31, 1972) to investigate the incidence of lung cancer. Seventy percent of the 125 men were aged 30 to 49 years at the start of the study. Ten percent had never smoked; 8% smoked cigars or pipe only; 5% were ex-smokers of cigarettes and 78% were current cigarette smokers. Twenty four percent smoked more than one pack per day.

Fourteen men left the investigation at various intervals during the five-year screening study because of job terminations. However, the survival status of 120 men among the 125, as of Dec 31, 1972, was determined through follow-up.

Workers were screened by means of chest photofluorograms and questionnaires regarding age, smoking habits and respiratory symptoms, at intervals averaging 8.5 months.

Exposure data was calculated as by DeFonso and Kelton (1976).

Remark : epidemiology study
Studies by Figueroa et al., (1973), Weiss and Boucot (1975), DeFonso and Kelton (1976), Pasternack, Shore and Albert (1977) and Collingwood, Pasternack and Shore (1987) were conducted on part of the same population.

Result : The incidence of small-cell carcinomas correlated with exposure index (time-weighted exposure rating multiplied by years of exposure from 1948 to 1972) and occurred in relatively young men. The study population did not develop cancer when the exposure index was less than 13.0. At an exposure index of 13.0-24.9, 17.2% developed cancer while at an exposure index >25.0, 30% developed cancer. Symptoms of chronic

bronchitis were reported more often among men exposed to CMME and a dose-response relationship was apparent with smoking a cofactor. Ventilatory function was not significantly affected by chemical exposure. Periodic screening over the first five years of the sutdy showed a decrease in chronic coughing and an increase in dyspnea while chemical exposure was diminishing.

Reliability : (2) valid with restrictions
2e

22.07.2004 (52)

Remark : epidemiology study
Studies by Figueroa et al., (1973), Weiss and Boucot (1975), DeFonso and Kelton (1976), Pasternack, Shore and Albert (1977) and Collingwood, Pasternack and Shore (1987) were conducted on part of the same population.

Result : A group of 125 men were studied beginning in Dec 1962 and followed for 5 years. Fourteen men were lost at various intervals because of job termination. In four of the remaining 111 men, lung cancer developed during the five-year period of observation. Eighty eight were in the age group from 35 to 54 and all four cases of lung cancer occurred in this group, giving a five-year incidence of 4.54%.

Concurrently a retrospective investigation of 14 lung cancers of workers exposed to chloromethyl methyl ether was made. Hospital records and autopsy results were examined and family physicians were interviewed. Ten of the 14 men smoked one package of cigarettes or more per day. One man smoked pipes only and three had never smoked. Histologic examination of 13 of the 14 lung cancers. Oat-cell carcinoma was found in 12 of 13 lung cancers examined histologically. The remaining individual had a squamous-cell carcinoma. This individual had only been exposed to CMME for one month according to a surviving co-worker. According to the company, this individual had no known exposure.

Reliability : (2) valid with restrictions
2e

22.07.2004 (53)

Method : A retrospective cohort mortality study was conducted on 6152 chemical workers (2460 exposed and 3692 non-exposed) engaged in chloromethyl ether manufacture. The cohort was composed of workers from 7 major U.S. companies from 1948 through 1980. Demographic information and work histories were obtained. Information on workers' smoking history was also requested.

Only two of the 7 companies had measured air concentrations of CMME. Despite the paucity of air concentration data, a rank order estimate of exposure intensity (i.e., score) by job classification was developed at each company. The exposure classification scheme reflected changes in CMME manufacturing processes, these changes impacting exposure levels at each company. Factors considered in the assignment of exposure scores included the changing proximity of jobs in relation to CMME operations, degree of enclosure, production-schedule frequency and quantity and prevailing wind patterns or air movement. It was not possible to assign actual concentrations to exposure scores or define relative differences between companies.

Remark : epidemiology study
Studies by Figueroa et al., (1973), Weiss and Boucot (1975), DeFonso and Kelton (1976), Pasternack, Shore and Albert (1977) and Collingwood, Pasternack and Shore (1987) were conducted on part of the same population.

Result : A total of 90 respiratory cancer deaths were observed, including 52 CMME

exposed workers and 38 CMME non-exposed workers. Among 32 exposed cases with respiratory cancer deaths with verifiable cell type, the highest proportion of cell types was oat cell (38%). In 20 non-exposed cases with respiratory cancer deaths, the highest proportion was adenocarcinoma (31%).

An increased incidence of respiratory cancers was observed at 2 of the 7 plants. These two plants were two of the three largest production facilities in this study. The third company was recognized as having a superior industrial hygiene program.

Reliability : (2) valid with restrictions
2e

22.07.2004 (54)

Method : A retrospective cohort mortality study was conducted on 10697 chemical workers (1827 exposed and 8870 non-exposed) engaged in chloromethyl ether manufacture. The cohort was composed of workers from 6 major U.S. companies from 1948 through 1972. Vital status and work histories were obtained. Of the 133 CME-exposed workers that have died, death certificates were obtained for 20 individuals.

Remark : epidemiology study
Studies by Figueroa et al., (1973), Weiss and Boucot (1975), DeFonso and Kelton (1976), Pasternack, Shore and Albert (1977) and Collingwood, Pasternack and Shore (1987) were conducted on part of the same population.

Result : Nearly half of the workers were employed at Firm 2.

An increased incidence of respiratory cancer and all malignant cancers was observed from Firm 2. This also resulted in an increased number of all malignant cancers for the total cohort. However the observed incidence of respiratory cancers and total malignant cancers at Firms 1, 3-6 was equal to the expected incidence.

Reliability : (2) valid with restrictions
2e

17.06.2003 (55)

Remark : Case report

Result : A case report of a chemist working with bis(chloromethyl) ether and CMME died 12 years after the last exposure to either material at the age of42. The concentration of either material the chemist was exposed to is unknown. The cancer appeared to be a type papanicolaou V.

Reliability : (2) valid with restrictions
2e

17.06.2003 (56)

Method : As part of regular medical check-ups, cytogenetic analysis of peripheral lymphocytes was conducted in workers.

Remark : peripheral lymphocytes

Result : A group of 12 workers with immunological changes also had cytogenetic analysis of peripheral lymphocytes. Scoring 200 cells/person an average of 6.7% aberrant cells were observed. Control values were only 2%. A repeat analysis was conducted in 10 of these 12 workers following their return from holiday. Cytogenetic analysis revealed only 3.1% aberrant cells following holiday.

No further information provided.

Reliability : (4) not assignable
4a

01.04.2003 (57)

Method : A cohort study was conducted among workers potentially exposed to CMME in a factory. The cohort consisted of all males employed at this factory between 1958 and December 31, 1986. A total of 1203 men, 258 (with 3785 person-years at risk) had worked in anion-exchange resin manufacture and had documented potential CMME/BCME exposure, while 945 (with 12,136 person-years) were never exposed. 92.2% of exposed and 87.5% of non-exposed workers were accounted for. Potential confounders were not examined in this study. Based on work histories, workers were rated on a scale of 0 to 6 in order of increasing magnitude. Cumulative dose was determined for each worker based on the score derived from the workers exposure history and years worked at that rating.

Remark : epidemiology study

Result : The lung cancer incidence of workers exposed to CMME/BCME was increased (Table 1).

Table 1
Incidence rates of lung cancer in workers in an anion-exchange plant

Median Cumulative Dose	Number of cases	Person years	SMR
0.5	0	341	0
2.5	1	1001	2.8
6.3	2	1034	4.9
12.5	2	746	16.7
24.0	2	254	40.0
40.0	4	408	18.2
Total	11	3784	

Cumulate dose = Sum of (exposure rating x years at that rating)

Reliability : (2) valid with restrictions
2e

23.04.2003 (58)

Method : A cohort study was conducted of 915 individuals from 11 plants which produced and/or processed chloromethyl ether in 8 cities in China. There were 534 males and 381 females in this cohort. These individuals were followed from the beginning of exposure to Dec 31, 1981 which resulted in 9707.5 person-years (6183 males and 3524.5 females).

The SMR of all causes of death was calculated on the basis of statistics of Shanghai.

Remark : epidemiology study
The data used to calculate the SMR was from the city of Shanghai which may or may not be representative of other areas of China.

Result : Thirty two deaths occurred during the study period. Among the fatalities, 20 were due to cancer in which 15 were lung cancer. In 11 of the 15 lung cancer cases, histopathological examination of the lung was performed. Of these 11, 8 (73%) were undifferentiated cell cancers and the remaining 3 were squamous cell carcinoma. The average age of death was 50 with a rage of 32 - 64. The interval from the year starting work to the diagnosis of lung cancer was 10 with a range of 2-20. The period of survival from diagnosis was 11.1 months on average with a range of 1-57 months. For the individuals with undifferentiated cell lung cancer the average survival period was 4.7 months.

Of the 8 plants examined, only 3 plants had an observed lung cancer with 12 lung cancers observed in one plant. Six of 14 lung cancer cases were

non-smokers (no indication give of the history of 15th person).

The SME for all causes of death was 197 (95% CI 130 - 300) compared to Shanghai.

Reliability : (2) valid with restrictions
2e

19.05.2003 (59)

Method : Blood samples were obtained from 77 workers occupationally exposed to bis(chloromethyl) ether and chloromethyl methyl ether. Simultaneously synthetic resin workers and subjects without any occupational exposure were used as controls.

After initial samples, workers were given ascorbic acid at daily doses of 1 g, 5 days/week for 5 months and percentage of chromosomal aberrations in peripheral blood was measured.

Remark : peripheral lymphocytes

Result : In the initial sample, the percentage of chromosomal aberrations was increased from control values prior to treatment with ascorbic acid (Table 1). After the 5 month treatment with ascorbic acid, the incidence of chromosomal aberrations had decreased but were slightly greater than control values.

Smoking habits had no clear cut effect on detected changes

Table 1
Effects of ascorbic acid treatment on chromosomal aberrations in BCME and CMME workers

	Initial sample	Final sample
Control	1.64%	1.88%
Synthetic resins workers	3.65%	3.52%
BCME and CMME workers	3.73%	2.13%

Reliability : (2) valid with restrictions
2e

02.08.2004 (60)

5.11 ADDITIONAL REMARKS

6.1 ANALYTICAL METHODS

6.2 DETECTION AND IDENTIFICATION

7.1 FUNCTION

7.2 EFFECTS ON ORGANISMS TO BE CONTROLLED

7.3 ORGANISMS TO BE PROTECTED

7.4 USER

7.5 RESISTANCE

8.1 METHODS HANDLING AND STORING

8.2 FIRE GUIDANCE

8.3 EMERGENCY MEASURES

8.4 POSSIB. OF RENDERING SUBST. HARMLESS

8.5 WASTE MANAGEMENT

8.6 SIDE-EFFECTS DETECTION

8.7 SUBSTANCE REGISTERED AS DANGEROUS FOR GROUND WATER

8.8 REACTIVITY TOWARDS CONTAINER MATERIAL

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10.1 END POINT SUMMARY

10.2 HAZARD SUMMARY

10.3 RISK ASSESSMENT